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WO 01/29003 A1

(54) Title: PROCESS FOR THE PREPARATION OF INTERMEDIATES USEFUL IN THE SYNTHESIS OF DIARYLPYRIDINES

(57) Abstract: A process for the preparation of intermediates useful in the synthesis of diarylpyridines having COX-2 inhibitor activity.

PROCESS FOR THE PREPARATION OF INTERMEDIATES USEFUL IN THE SYNTHESIS OF DIARYLPYRIDINES

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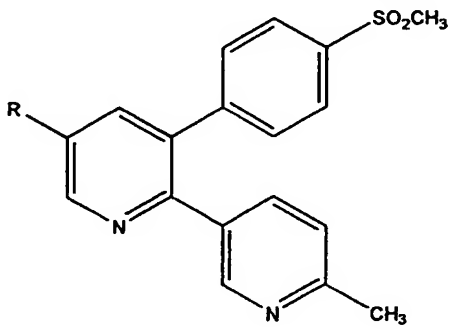
The present invention relates to a process for the preparation of intermediates useful in the synthesis of diarylpyridines and, more particularly, it relates to a process for the preparation of intermediates useful in the synthesis of compounds of formula

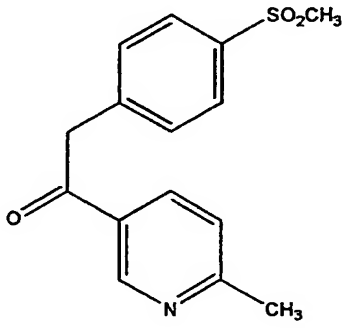


(I)

wherein R is chlorine, fluorine, bromine, iodine, CN or azide; useful as cyclooxygenase-2 (COX-2) inhibitors.

The compounds of formula (I) are described in the patent application WO 98/03484 (Merck Frosst Canada Inc.).

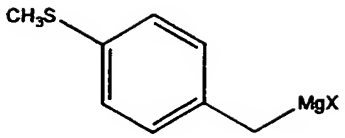
An improved process for the synthesis of the compounds of formula (I), recently described in the patent application WO 99/15503 (Merck & Co., Inc.), is characterized by the synthesis of the compound of formula



(II)

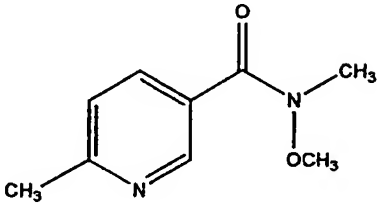
as key intermediate for the preparation of the COX-2 inhibitors of formula (I).

The synthesis of the intermediates (II) essentially consists of the reaction between a Grignard compound of formula

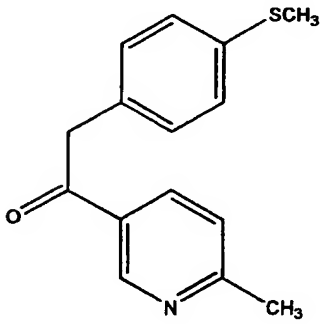


wherein X is chlorine, bromine or iodine;

and an amide (Weinreb amide) of formula



to yield a compound of formula



and of the subsequent oxidation.

This synthesis is undoubtedly advantageous in comparison with the known syntheses mainly because it avoids coupling reactions which require the use of expensive catalysts.

However, the used reagents, that is the Grignard compound and especially the amide, have several drawbacks.

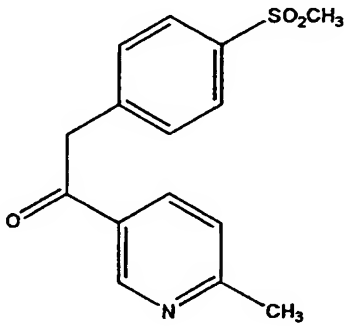
The Grignard compound must be prepared *in situ* from the corresponding 4-methylthio-benzyl halide.

Also the amide must be suitably prepared by reacting 6-methyl-nicotinic acid methyl ester with *N,O*-dimethyl-hydroxy-amine and isopropyl magnesium chloride in tetrahydrofuran, at -10°C.

It is clear that the process is not of easy industrial applicability because of the need to prepare the starting reagents (especially the amide) and because of the need to prepare the two Grignard reagents.

We have now found an improved and advantageous method for the preparation of the intermediates of formula (II) which overcomes all the drawbacks of the known processes.

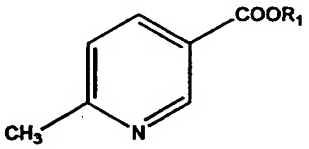
Therefore, object of the present invention is a process for the preparation of the intermediates of formula



(II)

comprising

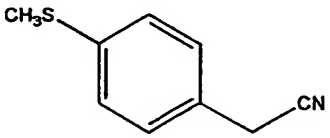
(a) the reaction between a 6-methyl-nicotinic acid ester of formula



(III)

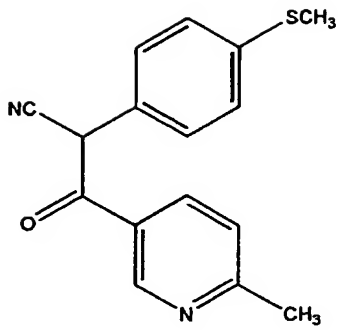
wherein R_1 is a linear or branched C_1-C_4 alkyl;

and (4-methylthio-phenyl)-acetonitrile



(IV)

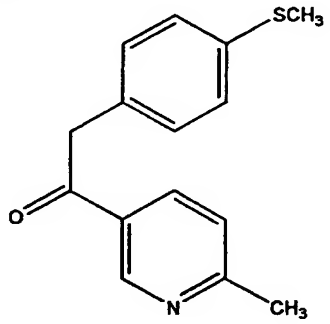
in the presence of a base and in a suitable solvent to give 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile



(V)

(b) the optional conversion of the compound (V) into a salt thereof with an organic or inorganic acid;

(c) the acid hydrolysis and the decarboxylation of the compound (V) or of the salt thereof to give the compound of formula

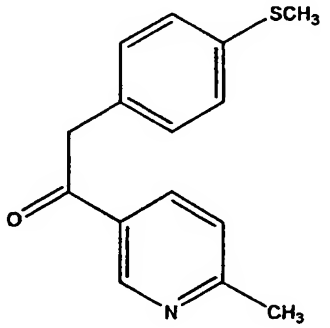


(VI)

(d) the subsequent oxidation of the compound (VI) to sulfone (II).

The process object of the present invention is useful for the preparation of intermediates of the synthesis of COX-2 inhibitors.

A preferred embodiment of the process object of the present invention is represented by the synthesis of



(VI)

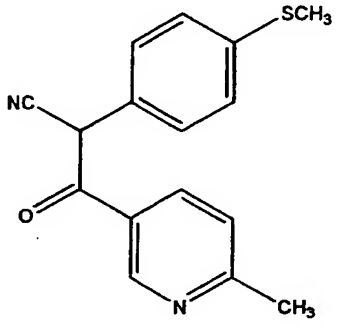
comprising

(a) the reaction between a 6-methyl-nicotinic acid ester of formula (III) and (4-methylthio-phenyl)-acetonitrile (IV) in the presence of a base and in a suitable solvent to give 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile

(b) the optional conversion of the compound (V) into a salt thereof with an organic or inorganic acid;

(c) the acid hydrolysis and the decarboxylation of the compound (V) or of the salt thereof.

A still more preferred embodiment of the present invention is represented by the synthesis of the compound of formula



(V)

or of a salt thereof with an organic or inorganic acid;

comprising the reaction between a 6-methyl-nicotinic acid ester of formula (III) and (4-methylthio-phenyl)-acetonitrile (IV) in the presence of a base and in a suitable solvent.

The compound 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile (V) and the salts thereof are new and are a further object of the present invention.

The 6-methyl-nicotinic acid esters useful in the process object of the present invention are methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and *sec*-butyl ester.

Preferably 6-methyl-nicotinic acid methyl ester is used.

In reaction *(a)* between a 6-methyl-nicotinic acid ester (III) and (4-methylthio-phenyl)-acetonitrile (IV), preferred bases are alkali or alkaline-earth metal C_1-C_4 alkoxide such as, for example, sodium methoxide, sodium *tert*-butoxide, potassium *tert*-butoxide and potassium *sec*-butoxide, lithium or magnesium amides such as, for example, lithium or magnesium 2,2,6,6-tetramethylpiperidine and lithium or magnesium diisopropylamine, and

hydrides such as sodium hydride.

Still more preferably sodium *tert*-butoxide or methoxide are used.

The base is generally used in excess with respect to the starting compounds (III) and (IV), preferably in a molar ratio from 1.2 to 1.8 with respect to (III).

Also the starting compound (IV) is used in excess with respect to the compound (III), preferably in a molar ratio from 1.1 to 1.4 with respect to (III).

Examples of preferred solvents for reaction *(a)* are toluene, dimethylsulfoxide, dimethylacetamide, N-methylpyrrolidone, dimethylformamide, tetrahydrofuran, alcohols and mixtures thereof.

Still more preferably toluene is used.

Generally the reaction temperature ranges from the room value to the boiling temperature of the reaction mixture, more preferably from 40°C to 90°C.

The optional conversion *(b)* is carried out by treating compound (V) with an organic or inorganic acid according to conventional techniques.

Preferably, hydrochloric acid is used, so obtaining the hydrochloride of compound (V).

The acid hydrolysis and the decarboxylation of the compound (V) or of the salt thereof is carried out according to known methods, preferably by heating in a mixture of hydrochloric acid and acetic acid.

The starting compounds of the process object of the present invention are known compounds. In particular, (4-methylthio-phenyl)-acetonitrile can be easy prepared from the corresponding chloride according to one of the methods described in the literature, for example by reaction with sodium cyanide (*Beilstein* EIV, 10, 563). The 6-methyl-nicotinic acid esters are commercially available or can be easy prepared from 6-methyl-nicotinic acid.

The oxidation reaction can be carried out following one of the methods already described in WO 99/15503. More preferably, the oxidation is carried out according to the method object of the co-pending Italian patent application entitled "Oxidation process for the preparation of intermediates useful in the synthesis of diarylpyridines" filed on the same date.

In order to better illustrate the present invention the following examples are now given.

Example 1

Synthesis of 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile

In a 1 liter reactor, equipped with mechanic stirrer, thermometer and dropping funnel, 6-methyl-nicotinic acid methyl ester (50 g; 87.2% titer; 0.289 moles), (4-methylthio-phenyl)-acetonitrile (60.9 g; 85.4% titer; 0.319 moles), dimethylsulfoxide (20.5 g) and toluene (82 g) were charged.

The resulting mixture was heated at 70°C before adding, in 1 hour, a solution of sodium *tert*-butoxide (39.8 g; 97% titer; 0.402 moles) in dimethylsulfoxide (41 g) and toluene (164.2 g).

At the end of the addition, the suspension was kept at 70°C under stirring for 1 hour and then cooled at 50°C.

Then, in 20 minutes, 31% HCl (118.6 g) was added.

After 10-15 minutes from the end of the addition a plentiful precipitate formed.

The suspension was cooled at 15°C and filtered after 20 minutes at this temperature. The obtained solid was washed with toluene (2 x 126.4 g) and then with acetone (115 g).

The product was dried in the air obtaining 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile hydrochloride (122.1 g; 48.5% titer as free base; 73% yield from 6-methyl-nicotinic acid methyl ester).

Example 2

Synthesis of 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile

In a 6 liter flask, equipped with mechanic stirrer, thermometer, dropping funnel, 6-methyl-nicotinic acid methyl ester (300 g; 1.99 moles) dissolved in toluene (615 g) was charged.

Then toluene (2142 g) and (4-methylthio-phenyl)-acetonitrile (319.9 g; 2.40 moles) were added.

The resulting mixture was heated at 70°C before adding sodium *tert*-butoxide (306.7 g; 3.19 moles), divided into five portions.

The resulting suspension was kept at 70°C for two hours and then was cooled at 20°C.

Keeping the temperature below 35°C, acetic acid (240 g) and, subsequently, acetone (906 g) were added.

The resulting suspension was diluted with water (610 g), cooled at 15°C and, after two hours at this temperature, was filtered on Buchner. The obtained solid was washed with water (2 x

195 g) and then with acetone (3 x 150 g).

The product was dried overnight at 60°C under vacuum obtaining 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile (439 g).

Example 3

Synthesis of 1-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-ethanone

In a 1 liter reactor, equipped with mechanic stirrer, thermometer and condenser, 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile hydrochloride (122.1 g; 48.5% titer as free base; 0.21 moles), acetic acid (179.7 g) and 31% HCl (433.7 g) were added.

The suspension was heated at 70°C and kept under stirring for about 16-18 hours. At the end of the reaction, the mixture was concentrated under vacuum up to obtain a residue weighing 227 g, then toluene (227 g) and 30% NaOH (126 g) were added, bringing the pH to a value from 4 to 7.

The resulting suspension was heated at 60°C and kept under stirring for 30 minutes. The phases were separated and the aqueous phase was extracted with toluene (2 x 75.6 g).

The collected organic phases were concentrated under vacuum at 60°C up to a residue weighing 253 g. Then the mixture was slowly cooled under stirring at 0°C.

The precipitated solid was filtered and washed with toluene (2 x 30 g).

After drying under vacuum, 1-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-ethanone (35.3 g; 65.4 % yield) was obtained.

Example 4

Synthesis of 1-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-ethanone

In a 5 liter reactor, equipped with mechanic stirrer, thermometer and condenser, 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile (439 g; 1.56 moles), acetic acid (700 g) and 31% HCl (1370 g) were added.

The suspension was heated at 80°C and kept under stirring for about 24 hours. At the end of the reaction, the mixture was concentrated under vacuum up to obtain a residual volume of about 1 liter. Then water (1350 g) was added and the pH was adjusted to 1.2-1.4 by adding 28% (w/w) ammonia (about 200 g).

Then ethyl acetate (370 g) was added and the pH of the mixture was brought to 4-4.5 by

adding 28% (w/w) ammonia (about 125 g).

This work up was carried out so that the temperature was kept between 40 and 45°C. The resulting suspension was then cooled at 0°C in two hours and, after 1 hour at this temperature, was filtered. The collected solid was washed with ethyl acetate (230 g) and water (500 g).

After drying at 60°C under vacuum up to constant weight, 1-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-ethanone (339 g; 66.4% molar yield from 6-methyl-nicotinic acid methyl ester).

Example 5

Synthesis of 6-methyl-nicotinic acid *n*-butyl ester

In a 300 ml reactor, equipped with mechanic stirrer, condenser and thermometer, kept under nitrogen, an aqueous solution of 6-methyl-nicotinic acid potassium salt (388.4 g; 6.4% titer, 0.142 moles) was charged.

The solution was heated and concentrated under reduced pressure up to a residue weighing 212.5 g, then cooled at room temperature.

The pH was brought to 9.5 (initial value of about 11) by adding glacial acetic acid (1.5 g) and then toluene (100 ml), Aliquat 336 (1.7 g; 0.0042 moles) and *n*-butyl bromide (39 g; 0.284 moles) were added, in that order, under stirring.

The mixture was heated under reflux (about 86-87°C) and kept at this temperature for 15 hours. After cooling at room temperature, the phases were separated and the organic phase was washed with 50 ml of water (washing pH = 9) and with further 50 ml of water (washing pH = 7). Water (100 ml) and, dropwise, 31% HCl (22 g) were added to the organic phase up to pH 1, keeping the internal temperature at 20-25°C.

The phases were separated and the organic phase was extracted with water (100 ml). After addition of 31% HCl (2 g) up to pH 1 (initial pH = 2), the phases were separated and the acid aqueous phases were collected. Toluene (100 ml) was added to the collected aqueous phases and, after cooling at 15°C, 30% NaOH (26 g) up to pH>12 was dropwise added in 20 minutes.

The phases were separated and the aqueous phase was washed with toluene (30 ml). The

collected organic phases were washed with water at pH 7 and concentrated to residue obtaining 6-methyl-nicotinic acid *n*-butyl ester (26.5 g; 98.8% HPLC titer; 95.6% yield).

Example 6

Synthesis of 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile

In a 300 ml reactor, equipped with mechanic stirrer and condenser, kept under nitrogen, 6-methyl-nicotinic acid *n*-butyl ester (25 g; 0.1285 moles), toluene (38 g) and (4-methylthio-phenyl)-acetonitrile (27.7 g) were charged.

The resulting mixture was heated at 70°C before adding portionwise, in about 50 minutes, a suspension of sodium *tert*-butoxide (20.8 g) in toluene (83 g) and dimethylsulfoxide (21.4 g). The resulting suspension was kept at 70°C for two hours, cooled at 40°C and slowly poured into 31% HCl (62 g), cooled at 5°C.

At the end of the addition water (47 g) was added, the mixture was cooled at 10-15°C, kept under stirring for 30 minutes and filtered by washing with toluene (2 x 29 g), with water (2 x 29 g) and subsequently with acetone (29 g), obtaining 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile (28.4 g; 79.7% HPLC titer; 62% yield).

Example 7

Synthesis of 1-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-ethanone

In a 300 ml reactor, equipped with mechanic stirrer, thermometer and condenser, under nitrogen, 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile (25 g; 0.0706 moles), glacial acetic acid (37.35 g) and 31% HCl (73.4 g) were charged.

The suspension was heated at 70°C and kept under stirring for about 24 hours. At the end of the reaction, the mixture was concentrated under vacuum up to a residue weighing 34.6 g. Then water (35 g) was added and the pH was adjusted to 7 by dropwise adding 30% (w/w) NaOH (27.4 g), in 20 minutes.

Then ethyl acetate (50 g) was added and the solution was heated at 65-70°C. The phases were separated at 70°C and the aqueous phase was washed with ethyl acetate (18 g) at 70°C. The collected organic phases were washed at 70°C with water (30 g), concentrated to a residue, which was taken up in ethyl acetate (40 g) at 70°C.

After cooling at 0°C in 4 hours and keeping this temperature overnight, the suspension was

filtered, washing with ethyl acetate (10 ml) and with cooled ethyl acetate (5 ml), obtaining 1-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-ethanone (15 g; 51.3% molar yield from 6-methyl-nicotinic acid *n*-butyl ester).

Example 8

Synthesis of 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile

In a 600 ml reactor, equipped with a reflux condenser, toluene (236 g), 6-methyl-nicotinic acid methyl ester (25.1 g; 99.5% titer; 0.1655 moles), (4-methylthio-phenyl)-acetonitrile (47.7 g; 59.5% titer; 0.1735 moles) were charged.

The resulting mixture was kept under nitrogen and heated at about 100°C before adding, in 30 minutes, a first portion of 30% sodium methoxide (3.3 g; 7.5% of the total amount). The temperature decreased to about 98°C (internal). After 30 minutes, a further portion of 30% sodium methoxide (3.3 g; 7.5% of the total amount) was added in about 30 minutes. The temperature decreased to about 94°C and a solid formed. After further 30 minutes, a third portion of 30% sodium methoxide (6.7 g; 15% of the total amount) was added as described for the previous additions and the temperature decreased to about 92°C. After 30 minutes, in about 4 hours, the remaining portion of 30% sodium methoxide (31.4 g) was added.

At the end of the addition the temperature was about 86°C. During the additions the solvent was distilled and collected. The distillation of the solvent was continued for about 6 hours (temperature 86÷87°C), then the reaction mixture cooled at about 20°C and, in about 30 minutes, glacial acetic acid (15.9 g) was added.

The addition was exothermic and the temperature was kept at 30÷35°C.

Then, acetone (75.2 g) in about 15 minutes and water (76 g) were added.

The resultant suspension was kept at 30÷35°C for 1 hour, then cooled at about 15°C in 1.5 hours to allow the crystallization of the product.

After 1 hour at 15°C the precipitate was filtered and washed with water (2 x 6 g) and then with acetone (2 x 5.0 g) obtaining wet 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile (56 g) used as such in the subsequent step.

Example 9

Synthesis of 1-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-ethanone

In a 600 ml reactor, water (21.0 g) and, keeping the temperature below 50°C, 66Bé sulfuric acid (56.5 g) were added. The reactor was equipped with a Marcusson and wet 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile (28 g) was charged at 35÷40°C.

The suspension was heated at 90°C and kept at this temperature up to complete dissolution.

The solution was cooled at 40°C and further wet 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile (28 g) was added.

The suspension was heated at about 115°C (internal). After 8 hours, the solution was cooled at about 60°C and water (47.0 g) was added.

Keeping the temperature from 40°C to 50°C, the pH of the reaction mixture was brought to 3.5÷4.0 by adding 30% ammonia (60.0 g) in about 2 hours.

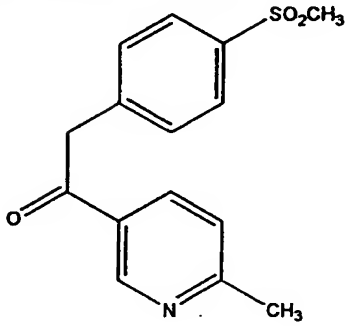
Ethyl acetate (55.6 g) was added to the resultant suspension and then the pH was brought up to a value from 4 to 5 by adding 30% ammonia (1.0 g) in about 30 minutes, keeping the temperature at 40÷50°C.

The suspension was kept at 40°C for about 30 minutes, then cooled at about 15°C in about 1 hour.

After 1 hour at about 15°C the suspension was filtered washing with ethyl acetate (2 x 17.6 g) and with water (2 x 45.6 g), obtaining, after drying under vacuum at 50°C, 1-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-ethanone (26 g).

Claims

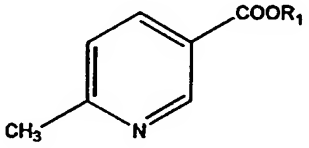
1) A process for the preparation of the intermediates of formula



(II)

comprising

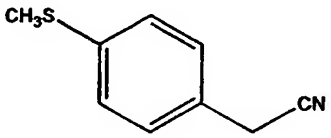
(a) the reaction between a 6-methyl-nicotinic acid ester of formula



(III)

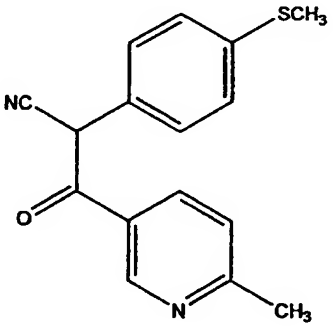
wherein R_1 is a linear or branched C_1-C_4 alkyl;

and (4-methylthio-phenyl)-acetonitrile



(IV)

in the presence of a base and in a suitable solvent to give 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile

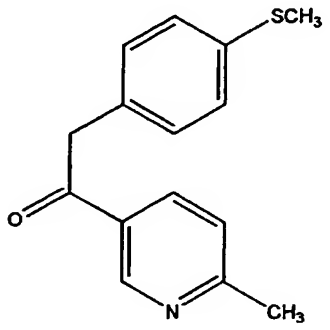


(V)

(b) the optional conversion of the compound (V) into a salt thereof with an organic or

inorganic acid;

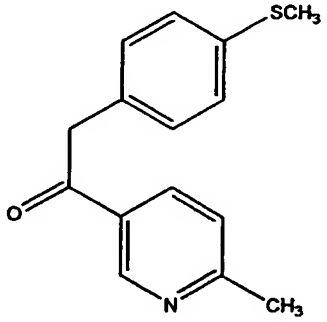
(c) the acid hydrolysis and the decarboxylation of the compound (V) or of the salt thereof to give the compound of formula



(VI)

(d) the subsequent oxidation of the compound (VI) to sulfone (II).

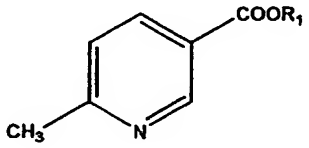
2) A process for the preparation of the intermediates of formula



(VI)

comprising

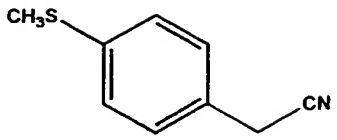
(a) the reaction between a 6-methyl-nicotinic acid ester of formula



(III)

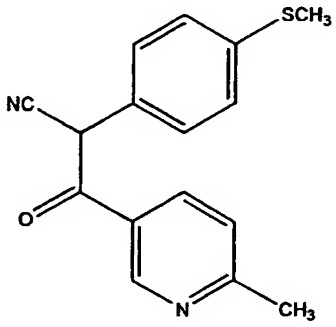
wherein R_1 is a linear or branched C_1-C_4 alkyl;

and (4-methylthio-phenyl)-acetonitrile



(IV)

in the presence of a base and in a suitable solvent to give 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile

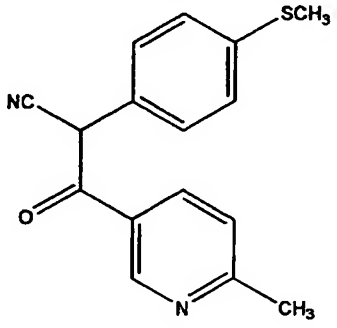


(V)

(b) the optional conversion of the compound (V) into a salt thereof with an organic or inorganic acid;

(c) the acid hydrolysis and the decarboxylation of the compound (V) or of the salt thereof.

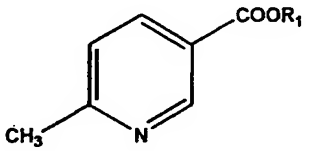
3) A process for the preparation of the intermediates of formula



(V)

comprising

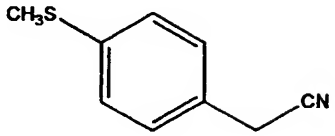
(a) the reaction between a 6-methyl-nicotinic acid ester of formula



(III)

wherein R_1 is a linear or branched C_1-C_4 alkyl;

and (4-methylthio-phenyl)-acetonitrile



(IV)

in the presence of a base and in a suitable solvent.

4) A process according to claims 1, 2 or 3 wherein the 6-methyl-nicotinic acid esters are methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or *sec*-butyl ester.

5) A process according to claim 4 wherein 6-methyl-nicotinic acid methyl ester is used.

6) A process according to claim 1, 2 or 3 wherein, in reaction *(a)*, the bases are alkali or alkaline-earth metal C_1-C_4 alkoxide, lithium or magnesium amides or hydrides.

7) A process according to claim 6 wherein sodium *tert*-butoxide or sodium methoxide are used.

8) A process according to claim 1, 2 or 3 wherein, in reaction *(a)*, the solvent is selected among toluene, dimethylsulfoxide, dimethylacetamide, N-methylpyrrolidone, dimethylformamide, tetrahydrofuran, alcohols and mixtures thereof.

9) A process according to claim 8 wherein the solvent is toluene.

10) A process according to claim 1 or 2 wherein the acid hydrolysis and the decarboxylation of the compound (V) or of the salt thereof is carried out by heating in a mixture of hydrochloric acid and acetic acid.

11) The compound 3-(6-methyl-pyridin-3-yl)-2-(4-methylthio-phenyl)-3-oxo-propionitrile and the salts thereof.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 00/09994

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/50 C07D213/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 15503 A (DAVIES IAN W ;GERENA LINDA (US); JOURNET MICHEL (US); LARSEN ROBER) 1 April 1999 (1999-04-01) page 22 -page 23; examples 3,4	1-11
Y	HALCZENKO W; SHEPARD K L : "Benzocycloheptapyridines. Analogs of Azatadine" JOURNAL OF HETEROCYCLIC CHEMISTRY., vol. 23, no. 1, 1986, pages 257-263, XP000985102 HETEROCORPORATION. PROVO., US ISSN: 0022-152X page 257, the first line of scheme 1 page 259, column 2, last paragraph -page 260, column 1, paragraph 2	1-11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2001	05/04/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 00/09994

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
E	WO 01 07410 A (LERESCHE JAMES EDWARD ;BESSARD YVES (CH); LONZA AG (CH); MERCK & C) 1 February 2001 (2001-02-01) the whole document	1-11

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Jonal Application No
PCT/EP 00/09994

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9915503 A	01-04-1999	AU 9500298 A	12-04-1999
		BR 9812837 A	08-08-2000
		EP 1023266 A	02-08-2000
		US 6040450 A	21-03-2000
WO 0107410 A	01-02-2001	NONE	